REMARKS

According to the Official Action claims 14 and 15 are rejected as being anticipated by Aggarwal (WO9709877). This rejection is respectfully traversed.

Anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference. *In re Paulsen*, 30 F.3d 1475, 31 USPQ 1671 (Fed. Cir. 1994). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Res. Found. v. Genentech, Inc.,* 927 F.2d 1565, 18 USPQ2d 1001 (Fed. Cir. 1991).

The Examiner's presumption that the underlying mechanism of "controlling neutrophil infilitration" is inherently present in Aggarwal et al. is incorrect. Aggarwal et al. does not guide, indicate nor show any experiment whatsoever which would lead to this conclusion. Inhibition of NF-kB by curcumin has been demonstrated by Aggarwal et al. in human cell line experiments. However, no experiment was carried out in animals or in humans. A dosage of 1 mg/kg to 100 mg/kg for controlling neutrophil infiltration has no support either directly or by reference from Aggarwal et al. or from the prior art.

The present invention demonstrates by in-vivo experiments that curcumin inhibits neutrophil infiltration in mice and this prevents or protects from septic shock conditions.

Neutrophil infiltration is a multistep process involving many known and unknown pathways. Any inhibition of any one or more of these pathways would cause the inhibition of neutrophil infilitration. NF-kB is a key factor that regulates one of the pathways. It works in concert with other transcription factors such as AP-1, CEBP and others.

Most importantly, neutrophil infiltration could also be inhibited without involving NF-kB. It has been shown that other pathways, without involving NF-kB could be blocked for inhibiting infiltration of neutrophils. Therefore, the Aggarwal et al. hypothesis that curcumin inhibits NF-kB activation and would therefore inhibit neutrophil infiltration is not valid. There are conditions where neutrophil infiltration may continue even if one inhibits NK-KB as has been clearly demonstrated in many references including the following:

Faouzi et al. JJ, et al. Anti Fas induces hepatic chemokines and promotes inflammation by an NF-kappa B-independent, caspase-3-dependent pathway. I. Biol. Chem. 2001 (Dec. 28: 276(52):49077-82. "Hepatic inflammation was also reduced by 70%. Taken together, these findings indicate that Fas ligation can induce inflammation in the liver in vivo. Inflammation does not arise from Fas-mediated signaling through NF-kappa B; rather, it represents indirect effect, requiring activation of caspase-3 and nuclear translocation of AP-1". **This reference directly states that inflammation due to neutrophil infiltration in the liver took place without NF-kB.6.**

Klumpp, D.J. et al. Uropathogenic Escherichia coli potentiates type 1 pilus-induced apoptosis by suppressing NF-kappa B. Infect. Immun, 2001 Nov: 69(11):6689-95. "Blocking NF-kappa B and thereby enhances type 1 pili-induced apoptosis as a component of the uropathogenic program." **In contrast to Aggarwal's hypothesis, here they have shown that blocking NF-kB aggravates inflammation that causes more pilus induced apoptosis.**

Joshi-Barve, S. et al. Inhibition of proteasome function leads to NF-kappa B-independent IL-8 expression IL-8 expression in human hepatocytes. Hepatology 2003. Nov.: 38(5):1178-87. "Decreased hepatocyte survival coincides with enhanced expression of IL-8, both at the protein and the messenger RNA (mRNA) levels. This increase in IL-8 is independent of nuclear factor kappa B (NF-kappa B) activation and is associated with an increase in c-Jun N-terminal kinase (JNK) and activator protein -I (AP-1) activity. **In conclusion, hepatocytes dying because of inhibition of proteasome function, produce massive quantities of the proinflammatory chemokine IL-8, possibly resulting in neutrophil infiltration increased inflammation and liver injury." This is another example of NfkB independent neutrophil infiltration.**

Therefore, since Aggarwal et al. does not teach each and every element of 1) a method for controlling neutrophil infiltration during inflammatory conditions caused by septic shock by administering to a subject in need thereof a pharmacologically effective dose of curcumin and 2) where the pharmacologically effective dose of curcumin ranges from 40mg/kg to 60 mg/kg body weight, claims 14 and 15 cannot be anticipated by Aggarwal et al.

Accordingly, it is respectfully requested that the rejection be withdrawn.

According to the Official Action claims 9-12 and 16 are rejected under 35 USC 103(a) as being unpatentable over Aggarwal (WO 9709877) in view of Ammon (US Patent 5,401,777). This rejection is respectfully traversed.

As the Examiner states on page 5 of the Official Action, the prior art does not disclose the underlying pharmacological mechanism of curcumin in "controlling neutrophil infiltration." Aggarwal does not disclose nor suggest a method for the treatment of septic shock conditions comprising administering to a subject in need thereof orally at specified time intervals a dosage of curcumin in the range of from 40 mg/kg to 60 mg/kg of body weight which is effective to prevent neutrophil infiltration from blood vessels to underlying tissues. As explained above there are conditions where neutrophil infiltration may continue even if one inhibits NF-kB so that it is not obvious from Aggarwal to treat septic shock by preventing neutrophil infiltration.

Since the primary reference does not disclose nor suggest the claimed invention, the disclosure of the secondary reference in combination with Aggarwal does not make the claimed invention obvious.

It is respectfully requested that the rejection be withdrawn.

According to the Official Action claims 13 and 17 are rejected under 35 USC 103(a) as being unpatentable over Aggarwal (WO 9709877) in view of Schneider (US Patent 6,013,273). This rejection is respectfully traversed.

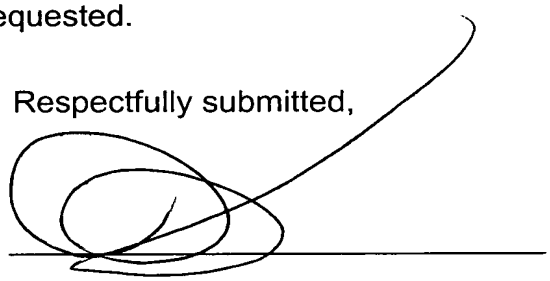
As the Examiner states on page 6 of the Official Action, the prior art does not disclose the underlying pharmacological mechanism of curcumin in "controlling neutrophil infiltration." Again as explained above there are conditions where neutrophil infiltration may continue even if one inhibits NF-kB so that it is not obvious from Aggarwal to treat septic shock by preventing neutrophil infiltration.

Again since the primary reference Aggarwal does not disclose nor suggest the claimed invention, the disclosure of Schneider in combination with Aggarwal does not make the claimed invention obvious.

It is respectfully requested that the rejection be withdrawn

It is submitted that this application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,



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